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| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

**DATE MAILED:** 09/24/98

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/931,219 | Applicant(s) Falo et al. |
|---|---|---|
| | Examiner Jill D. Martin | Group Art Unit 1632 |

☒ Responsive to communication(s) filed on *May 8, 1998* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-3, 5-17, 19-32, 34-47, 49-61, and 63-67* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5-17, 19-32, 34-47, 49-61, and 63-67* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. (Substitute)

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948 (Substitute)

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

Applicants' Preliminary Amendment filed May 8, 1998, Paper No. 18, has been entered. Claims 4, 18, 33, 48 and 62 have been canceled. Claims 1, 5, 15, 19, 29, 34, 44 49, 59 and 63 have been amended. Claims 1-3, 5-17, 19-32, 34-47, 49-61 and 63-67 are pending and under current examination.

### *Priority*

This application filed under former 37 CFR 1.62 lacks the necessary reference to the prior application. A statement reading "This is a file wrapper continuation of Application No. 08/535,556, filed September 28, 1995" should be entered following the title of the invention or as the first sentence of the specification. Also, the current status (now abandoned, now US Patent No., etc.) of the parent nonprovisional application(s) should be included in the above statement.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-17, 19-32, 34-47, 49-61 and 63-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods, wherein the mammalian host is a mouse, the antigenic protein is OVA, and the treatment is defined as immunization against melanoma (treatment occurs prior to the onset of tumors), does not

reasonably provide enablement for the claimed methods providing treatment in the form of an elicited immune response to a mammalian hosts (humans) afflicted with a naturally occurring disease, e.g., cancer, AIDS, etc., wherein often the disease evades immune system recognition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue numerous articles discuss the use of mouse tumor models and/or OVA antigens demonstrating that Applicants' methodologies would be accepted by those skilled in the art as providing representative and reliable data. Page 4 of the Preliminary Amendment. Applicants further argue that they have submitted evidence directed to the expression of the reporter gene GFP in mice and indicate that such evidence should be sufficient to enable all antigens. See page 5 of the Preliminary Amendment. Applicants argue that they present evidence that human APCs are capable of uptake and expression of yet a third antigen, *lacZ*, *in vitro*, thus, Applicants conclude that in view of their mouse data, they have demonstrated that human APCs will express antigens *in vivo*. In summary, Applicants submit that clear and convincing data that would be accepted by one skilled in the art has been presented to support enablement of the present invention. Please note that the Examiner has focused on Applicants' arguments most closely pertaining to the following scope rejection rather those pertaining to the enablement rejection set forth in the prior Office actions.

Applicants' broad claims read on treatment (elicitation of an immune response) to any mammalian host, in particular to human hosts (see in particular claims 2, 16, 30, 45 and 60). Please note that Applicants' claims recite the elicitation of an immune response, however, in light of the specification such a response is clearly directed to providing protective immunity. For example, the specification discloses their present invention as a genetic immunization protocol which stimulates antigen-specific CTL mediated immunity and in turn promotes direct destruction of specific neoplastic or virally infected cells within the host. See page 4, lines 22-26. As such, it is not clear as to the purpose of an immune response without protective immunity. Please note that the claims are to be given their broadest reasonable interpretation that is consistent with the specification. To this regard, while Applicants' evidence provides a reasonable correlation to achieving elicitation of an immune response in a host mammal and even anti-tumor immunity in a mouse model in response to the OVA antigen; Applicants' evidence does not provide a reasonable correlation to achieving protective immunity in host mammals afflicted with naturally occurring cancers which have evaded immune system recognition or any virally induced diseases. Applicants' evidence provided in the specification and in the Falo Declarations, filed December 9, 1996 and May 8, 1998, Paper Nos. 9 and 17, respectively, is directed to anti-tumor immunity in mice, marker gene GFP expression in mice, or marker gene (*lacZ*) expression in human dendritic cells *in vitro*. Please note that is well known in the art that marker genes do not stimulate CTLs and merely demonstrate expression which can be assayed for such that minimal levels can be detected. As such, Applicants' mouse B16/OVA tumor model provides evidence pertaining to

the claimed invention. However, Applicants' broad claims read on protective immunity from any and all viral pathogens. See claims 12-14, 26-28, 41-43, and 56-58. Applicants' broad claims even read on protective immunity to Hepatitis C virus. However, Nakano et al. (Journal of Virology, 1997) teach that different routes of injection of HCV E2 plasmids can result in quantitatively and qualitatively different humoral immune responses in mice and further report that "it remains to be seen whether nucleic acid-based immunization could result in the induction of such antibodies in a susceptible animal model", with respect to HCV.

Applicants' evidence is directed to anti-tumor immunization in a melanoma mouse model. However, Applicants' claimed methodology is specifically directed to providing protective immunity in humans. The importance of relevant animal models for support of enablement is imperative in the determination for effectiveness of gene therapy. This is supported by Orkin et al. in the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (see pages 10-11 and 14). On page 11, second and third paragraphs, Orkin et al. emphasize the importance of relevant animal models, and state that many "mouse models often do not faithfully mimic the relevant human conditions." Orkin et al. also indicate that when dealing with cancer, the relevance of animal models appears to be less predictive than with other single-gene disorders. With regard to animal models for cancer vaccines, Hanania et al. support this notion by indicating differences in cancer patients and animal models. For example, Hanania et al. disclose that the balance between the tumor and its host is far different when comparing cancer patients (often between 100 million to 10 billion tumor cells) and animal models (below 1

million tumor cells). In addition, Hanania et al. point out that "[i]n animal models, the tumor vaccine is used in animals that have never been exposed to the tumor, whereas in the clinical trials of tumor vaccines in humans, the vaccines are being tested in patients in whom the tumor has been present for months or years." Hanania et al. report that in light of this observation, those of skill in the art predict that T cells to tumors in such patients will become tolerant or nonreactive, and thus, will not likely attack and kill tumor cells as often demonstrated in experimental animal models, i.e., immunocompetent animal models. (See page 542, paragraph bridging columns 1 and 2). Furthermore, it is well known in the cancer art that tumor cells are known to evade immune surveillance through the production of immunosuppressive cytokines (Culver, British Medical Bulletin, 1995, page 195, second paragraph) and that researchers tend to focus their studies on treatment of melanoma, colorectal cancer and renal cell carcinoma since these tumors are more amenable to immunologic manipulation than other solid tumors (page 194). Thus, more evidence is necessary to provide a nexus between Applicants' tumor model and genetic immunization in humans afflicted with neoplastic diseases of various tumor types.

With regard to the methodology of the invention, Barry et al. (Vaccine, 1997) report that several parameters affect the outcome of genetic immunization. Such parameters are not addressed by Applicants melanoma OVA mouse model. For example, Barry et al. disclose that the intracellular biology, expression level and toxicity of the antigen employed, and the genotype and age of the animal employed, are the most predominant parameters which affect achieving protective genetic immunity. Specifically, Barry et al. discuss the inverse relationship between

expression levels and CTL responses for antigens bearing CTL epitopes (e.g., HIV gp160). Such a parameter is not addressed in Applicants' specification, although such an embodiment is specifically claimed. With regard to mouse models, Barry et al. report that the gene expression directly correlates with the level of immune responses observed, suggesting that in older mice, the immune response would be reduced. As such, these observations suggest that immune responses would be greatly reduced in adult human hosts afflicted with progressive cancer which has evaded immune system recognition. Applicants fail to address this parameter although Applicants claims read on such an embodiment. Thus, Applicants fail to provide parameters and/or conditions under which the instant invention would reasonably provide protective anti-tumor or viral immunity in adult human hosts already afflicted with neoplastic or virally-induced diseases. The claimed invention is clearly directed to such an embodiment.

Furthermore, the courts have stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Thus, it is maintained that the specification fails to teach how to practice the claimed methods, as written, and when taken as a whole, such that the claimed methods provide protective anti-tumor or anti-viral immunity in a mammal, in particular a human which is afflicted with a naturally occurring disease which has evaded immune system recognition. Applicants fail to provide sufficient guidance and direction for carrying out their claimed methods as broadly claimed such that protective immunity can be achieved in any and all mammalian hosts against any and all types of neoplastic or virally infected cells. Such evidence is necessary to enable the claimed methods, in particular in view of the lack of evidence for protective viral immunity in any mammalian host and clear discrepancies between cancer vaccine mouse models and human cancer patients, in particular at the time the invention was filed.

Therefore, claims 1-3, 5-17, 19-32, 34-47, 49-61 and 63-67 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement for the broad scope of the claims.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 15 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by either of Tang et al. (Nature, 1992) or Barry et al. (Biotechniques, 1994).

The claimed invention is directed to a method of genetic immunization, wherein in the inoculation step is either direct injection or by a biolistic device or both. Tang et al. teach a method for eliciting an immune response in a mouse by introducing a gene encoding the protein into the skin of the mouse by the biolistic system which can propel DNA-coated gold microprojectiles directly into the cells of the mouse. See Abstract. Barry et al. teach a method for eliciting an immune response defined as the production of antibodies in a mouse. The method of Barry et al. teach the biolistic transfection of cells of the mouse with human growth hormone (hGH) and the production of high levels of polyclonal antibodies against human growth hormone as a result of the immunization. See Abstract. The method of Tang et al. or Barry et al. meet all of the limitations of claims 1, 15 and 29.

Thus, claims 1, 15 and 29 are clearly anticipated by either of Tang et al. or Barry et al.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 15 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Hui et al. (Journal of Immunological Methods).

Hui et al. teach a method for the genetic H-2kb immunization of mice by means of a biolistic system directly inoculating host spleen cells and report the efficient generation of anti-H-

2kb allo-reactive CTL. The method of Hui et al. meets all of the limitations of claims 1, 15 and 29.

Thus, Hui et al. clearly anticipates claims 1, 15 and 29.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 15, 29, 44 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner et al. (US Patent 5,593,972) taken with either of Tang et al. or Barry et al.

Weiner et al. teach methods of genetic immunization in mice using target antigens of interest. Weiner et al. discuss that the mechanism of action behind the immune response elicited by the target protein involves antigen presentation which in turn stimulates CTL responses. See column 8, lines 37-51. Specifically, Weiner et al. teach the use of mouse models designed by using tumor cells that specifically express a foreign target protein. Weiner et al. report results which clearly demonstrate that the genetic vaccine produced a broader, more effective immune response which was capable, by virtue of CTL's, of completely eliminating tumors. See column 27, lines 1-47. Weiner et al. teach the use of genetic vaccines such as DNA encoding HIV gp160

(Example 3) and DNA encoding the human neu oncogene (Example 25). Weiner et al. also discuss that their methods can entail *in vivo* or *ex vivo* administration of the genetic vaccine. See column 8, lines 22-25. Weiner et al. differ from the claimed invention in that they do not specifically teach the construction of DNA vaccines or particulate polynucleotides for use in particle bombardment. However, Weiner et al. propose that increased efficiency of their genetic vaccination system may be achieved by use of a direct DNA delivery system such as particle bombardment. See column 32, lines 55-57. Furthermore, at the time the claimed invention was made, Tang et al. and Barry et al. teach methods of genetic vaccination in mice by means of particle bombardment. Tang et al. and Barry et al. are described *supra*.

Accordingly, in view of the teachings of Tang et al. and Barry et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method of Weiner et al. by employing particulate polynucleotides and/or particle bombardment for introducing the genetic vaccine into cells for antigen presentation and elicitation of an immune response against a target antigen in mice.

Thus, the claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

### *Conclusion*

Claims 2, 3, 5-14, 16, 17, 19-28, 30-32, 34-43, 45-47, 49-58, 60, 61 and 63-67 appear to be free of the prior art of record, however are subject to another rejection. Please note that

claims 2, 3, 5-14, 16, 17, 19-28, 30-32, 34-43, 45-47, 49-58, 60, 61 and 63-67 appear to be free of the prior art of record because the claims are specifically directed to methods of genetic immunization in humans and the prior art does not teach or suggest methods of human genetic immunization with a reasonable expectation of success.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Whalen et al., Clinical Immunology and Immunopathology (April 1995), Vol. 75, pages 1-12, See Abstract.

Boon et al., Annual Review of Immunology (1994), Vol. 12, pages 337-365, See Abstract.

Kawakami et al., Journal of Immunology (April 15, 1995), Vol. 154, pages 3961-3968, See Abstract.

Frey et al., Clinical Immunology and Immunopathology (November 1993), Vol. 69, pages 223-233, See Abstract.

Appleman et al., International Journal of Cancer (June 9, 1995), Vol. 61, pages 887-894, See Abstract.

Johnston et al., Methods in Cell Biology (1994), Vol. 43, pages 353-365, See Abstract.

Klein et al., Current Opinion in Biotechnology (October 1993), Vol. 4, pages 583-590, See Abstract.

**Please note that the last name of the Examiner of record has changed from Jill Schmuck to Jill Martin.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jill Martin whose telephone number is (703)305-2147.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached on (703)308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

**The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.**

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Jill D. Martin

September 20, 1998